## REMARKS

The February 29, 2008 Official Action has been carefully considered. In view of the present amendment and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the February 29, 2008 Official Action. The initial due date for response, therefore, was May 29, 2008. A petition for a three (3) month extension of the response period is submitted with this amendment and request for reconsideration, which is being filed before the expiration of the three (3) month extension period.

This application is entitled to small entity status. Therefore, the extension fee is being paid at the small entity rate.

In the February 29, 2008 Official Action, claims 1, 3 and 11 stand rejected as allegedly anticipated by published International Publication No. WO 99/38508 A1 of Nitz et al.

Claims 1-33 have been rejected under 35 USC §103(a), as allegedly unpatentable over Nitz et al., supra, considered in view of K. Avis, Pharm. Dosage Forms, Vol. 1: Parenteral Medications, 173-175 (1992), which is referred to in the Official Action as DeLuca et al. In support of this rejection, the examiner asserts that the some of the instantly claimed compounds are positional isomers of the compounds disclosed in WO 99/38508. DeLuca et al. is cited for its disclosure of useful carrier vehicles for parenteral formulations. According to the examiner, the subject matter of claims 1-33 is *prima* facie obvious because one of ordinary skill in the art would expect that isomers of the compounds disclosed in WO 99/38508 would be capable of treating pneumovirus.

Claims 34 and 35 have been further rejected under 35 USC §103(a) as allegedly unpatentable over WO 99/38508. The examiner acknowledges, at page 8 of the February 29 Official Action, that WO 99/38508 does not "specifically teach where $R_1'$ and $R_1''$ are as defined in the instant claims". The examiner nonetheless contends that WO 99/38508 teaches a compound where R is pyridine in the final product and that by going through Scheme A, compounds which correspond to where $R_1'$ and $R_1''$ are HET would be generated. Accordingly, the examiner considers claims 34 and 35 to be *prima facie* obvious.

The foregoing rejections constitute all of the grounds set forth in the February 29, 2008 Official Action for refusing the present application.

In accordance with the present amendment, the structure of Formula I in claim 1 has

been deleted and replaced with the structure of Formula Ia from claim 2. Support for this amendment of claim 1 is provided at pages 5-7 of the present specification. In addition, the "whereby" clause in the definition of HET in claim 1 has been deleted because it is considered inconsistent with specific embodiments of the invention that are exemplified and claimed in the present application. See Examples 4, 5, 32 and 36 and claim 7.

Claims 34 and 35 have been amended in a manner similar to claim 1.

As a result of the present amendment to claim 1, claims 2, 3 and 5 have been cancelled. The deletion of structural Formula I from claim 1 and the cancellation of claims 3 and 5 should not be construed as indicative of applicants' concurrence or acquiescence in the several prior art rejections thereof in the February 29, 2008 Official Action, or otherwise as an abandonment of applicants' efforts to secure patent protection on the deleted or cancelled subject matter. On the contrary, this claimed subject matter has been cancelled without prejudice to applicants' right to file one or more continuing applications directed to the cancelled subject matter, as provided under 35 USC §120.

No new matter has been introduced into this application by reason of the foregoing claim amendment, entry of which is respectfully requested.

As a result of the present amendment of claim 1, and the cancellation of claim 3, the 35 USC §102(b) rejection of claims 1, 3 and 11 has been overcome because WO 99/38508 fails to identically describe the compounds now claimed in claim 1. Thus, the only matters remaining to be addressed are the 35 USC §103(a) rejections of claims 1-33 as allegedly unpatentable over the combined disclosures of WO 99/38508 and DeLuca et al, and of claims 34 and 35, as allegedly unpatentable over WO 99/38508, standing alone. For the reasons given below, the last-mentioned grounds of rejection are respectfully traversed.

### A. The Impropriety of the 35 USC §103(a) Rejection of Claims 1-33 Based on WO 99/38508 and DeLuca et al.

In view of the recent opinion of the Court of Appeals for the Federal Circuit in *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007), the 35 USC §103(a) rejection of claims 1-33 based on the combined disclosures of WO 99/38508 and DeLuca et al. is plainly improper and should, therefore, be withdrawn upon reconsideration.

Considering first the compound claims, *per se*, i.e., claims 1-10, all of these claims call for meta-substitution by the $R_1$ group. By contrast, all of the compounds described in

WO 99/38508 having the triphenylmethylene structure are para-substituted on the phenyl rings. Thus, there is a clear structural difference between the compounds of applicants' claims 1-10 and the compounds described in WO 99/38508. Moreover, WO 99/38508 fails to provide any reason or motivation for one of ordinary skill in the art to arrive at compounds having meta-substituted $R_1$ groups, as required in claims 1-10. Consequently, WO 99/38508 cannot reasonably be found to render the compounds claimed by applicants herein *prima facie* obvious, according to the test applied by the Federal Circuit in *Takeda, supra*. In that case, the Court stated that a finding of *prima facie* obviousness of a chemical compound requires that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. The Court went on to comment in this regard, as follows:

> That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*. While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant art to combine the elements in the way the claimed new invention does" in an obviousness determination, *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound. [footnote omitted; emphasis added].

In rejecting the defendant's obviousness argument in *Takeda*, the Court adopted the District Court's finding that there was "nothing in the prior art to suggest making the specific molecular modifications to [the most closely related prior art compound] that are necessary to achieve the claimed compounds". *Id.* at 1177. The molecular differences between the compounds claimed by applicants herein and those of WO 99/38508 are at least as patentably significant as those found to exist in *Takeda* (5-{4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione vs. 5-{4-[2-(6-methyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione).

Moreover, in the present case, just as in *Takeda*,. there is no disclosure in the cited prior art to suggest to an artisan of ordinary skill that meta- versus para-substitution on the phenyl ring of the methylene bisphenol compounds called for in claim 1 would bring about a

reasonable expectation of success.

The argument advanced by the examiner in support of this rejection is untenable for the additional reason that the cited references fail to support the legal conclusion that the claimed compounds (as well as their compositions and methods of use) are unpatentable according to the obviousness standard of 35 USC §103(a). It has long been held that a rejection under 35 USC §103 is proper only when the invention as a whole is shown to be obvious in view of the prior art. Moreover, since chemical compounds are inseparable from their properties, the properties of a claimed compound must also be considered as a part of the invention as a whole in assessing patentability under 35 USC §103(a). *In re Albrecht*, 185 USPQ 585 (CCPA 1975).

It is stated at page 7 of the present specification that:

> The preferred compound of Formula I(a) has improved solubility in pharmaceutical formulations. In particular, the compounds of Formula I(a) have improved solubility in ethanolic solvents. The indicated improved solubility characteristics facilitate the preparation of pharmaceutical formulations and the delivery of the pharmaceutical formulations to a patient's pulmonary system using electrohydrodynamic (EHD) technology. Electrohydrodynamic spraying is a known process whereby solutions are aerosolized using electrical forces. In an EHD spray nozzle, the fluid to be aerosolized flows over a region of high electric field strength and receives a net electrical charge that remains on the surface of the fluid. As the solution exits the nozzle, the repelling force of the surface charge generates a thin jet of fluid. The jet breaks up into droplets of uniform size that collectively form a cloud. The result is an aerosolized solution having a monodispersed particle size distribution and near zero velocity. The improved solubility of the compound of Formula I(a) in the formulations used in an EHD device facilitates the delivery of higher concentrations of the desired compound to the patient pulmonary tissue with fewer numbers of actuations of the EHD device. One of ordinary skill in the art may practice the instant invention with EHD devices that are commercially available or otherwise with known EHD technology.

See also pages 28-29 of the present specification which provides additional disclosure regarding formulation of the claimed compounds.

Applicants consider it not only unexpected, but, indeed, quite surprising that the solubility characteristics of the meta-substituted compounds claimed in claims 1-10 are so dramatically improved with respect to pulmonary administration.

The improved solubility characteristics of the meta-substituted compounds of the present invention, as compared to the triphenylmethylene compounds disclosed in WO 99/38508 that are substituted at the para-position, could not have been predicted.

This improved solubility was certainly not predictable from the disclosure of WO 99/38508. Moreover, the consequences of such an unexpected improvement in solubility using ethanolic solvents are therapeutically significant. The surprising improvement in solubility in ethanolic solvents observed for the meta-substituted compounds of the present invention allows for efficient and effective pulmonary delivery of a therapeutic dose of the compounds of the invention.

The artisan of ordinary skill would not find in DeLuca et al. any useful guidance that pertains to pneumovirus drug formulations for pulmonary delivery, and certainly not the advantage to be gained in this connection by administering the meta-substituted compounds of the present invention, as compared to the para-substituted compounds of WO 99/38508. DeLuca et al. teaches only general principles concerning one particular mode of parenteral drug delivery, i.e., drug preparations for administration by hypodermic injection.

In summary, the combined disclosures of WO 99/38508 and DeLuca et al. plainly fail to establish the *prima facie* obviousness of claims 1-33. The case law cited in support of this rejection does not compel a contrary conclusion. First of all, *In re Norris,* 84 USPQ 458 (CCPA 1950) and the cases discussed therein pre-date *In re Papesch*, 137 USPQ 43 (CCPA 1963) which established, as an enduring principle of patent law, that the patentability of chemical compounds does not depend solely on the similarity between the structure of the claimed compounds and that of a prior art compound, but rather the non-obviousness of its properties must also be considered. It is also noteworthy that neither the *Norris* case nor *In re Jones*, 74 USPQ 152 (CCPA 1947), which is cited in *Norris*, relates to therapeutic compounds, compositions or methods, in which solubility is an extremely important property given its substantial influence on drug bioavailability. *In re Wood*, 199 USPQ 137 (CCPA 1978) did not address the obviousness of positional isomers.

### B. The Impropriety of the 35 USC §103(a) Rejection of Claims 34 and 35 Based on WO 99/38508

This ground of rejection is based on a demonstrably false premise, which is that by using Scheme A, at page 7 of WO 99/38508, compounds would be generated wherein $R_1'$ and $R_1''$ are HET. However, the R substituent of the reactants in Scheme A, as "previously defined", does not include HET. See page 4 of WO 99/38508,

where R is defined as "a radical selected from the group of hydrogen, hydroxy, alkoxy, alkyl, halogen, nitro or alkoxy monosubstituted with a substituent selected from carboxy, amino, monoalkylamino, dialkylamino or acetamido".

Furthermore, claims 34 and 35 have been amended in a manner similar to claim 1, such that the structural formulas recited therein are meta-substituted by the $R_1'$ and $R_1''$ groups, respectively. As such, this structural feature of the intermediates claimed in claims 34 and 35 is a contributing cause of the unexpectedly improved solubility characteristic of the final products produced from these intermediates, as discussed above.

The capacity of an intermediate to contribute to an end product to have a property that is unexpectedly superior to that of a prior art end product is a property which inures to the benefit of the intermediate and which is to be considered as part of the "subject matter as a whole" in determining the non-obviousness of the intermediate. *In re Magerlein*, 202 USPQ 473, 478-479 (CCPA 1979). According to the rationale of *Magerlein*, therefore, the intermediates of claims 34 and 35 must be considered patentably distinct over the intermediates disclosed in WO 99/38508. The §103(a) rejection of claims 34 and 35 as unpatentable over WO 99/38508 should, therefore, be withdrawn upon reconsideration.

In reconsidering this application, the examiner is requested to bear in mind that granting a patent on applicants' invention will in no way diminish the availability of pneumovirus treatments available to the public. The claims of this application would not preclude public access to the compounds described in WO 99/38508 administered in the manner described therein. Nor do the claims presented herein preclude utilization of the compounds described in WO 99/38508 when formulated according to the teaching of DeLuca et al. Applicants' claims 1-33 cover only their particular meta-substituted compounds or compositions containing such compounds and the use thereof in treating pneumovirus infection.

Lastly, the examiner is correct in presuming (at page 3 of the February 29, 2008 Official Action) that the subject matter of the various claims was commonly owned at the time the inventions covered thereby were made.

In view of present amendment and the foregoing remarks, it is respectfully requested that the rejections set forth in the February 29, 2008 Official Action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

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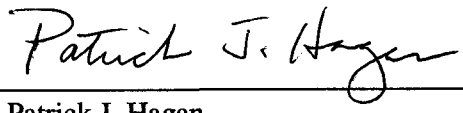
By 

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